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Clinical Study

Assessment of sleep satisfaction in patients with dementia due to Alzheimer's disease

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ABSTRACT

Sleep length and architecture are potential markers of progressive cognitive impairment, while neuropsychiatric symptoms and APOE4− haplotypes have been associated with more sleep complaints in patients with dementia due to Alzheimer's disease (AD). In this cross-sectional study, we sought to investigate which factors might be related to sleep satisfaction in patients with AD. A total of 217 consecutive patients with AD were assessed for demographic features, neuropsychiatric symptoms, cognitive decline, functional impairment for activities of daily living, caregiver burden, APOE haplotypes, self-reported sleep satisfaction and length of sleep. Statistical comparisons were conducted with significance at $p < 0.05$. Concerning sleep complaints, 179 patients (82.5%) reported satisfactory sleep, while 38 (17.5%) were unsatisfied, with no relation to age, sex, APOE haplotypes, obesity, education, marital status, alcohol consumption or smoking found. Length of sleep ($p = 0.011$) and behavioural symptoms ($p = 0.009$) had significant associations with sleep satisfaction. Length of sleep was positively correlated with apathy ($p = 0.014$) and scores on the Clock Drawing Test ($p = 0.015$), and inversely correlated with anxiety ($p = 0.015$) and independence for instrumental activities of daily living ($p = 0.003$). Patients who were treated with memantine ($p = 0.02$) or anti-psychotics ($p < 0.01$) had longer duration of sleep. In conclusion, behavioural symptoms had strong associations with sleep satisfaction, which is highly correlated with length of sleep in patients with AD. Functional independence, apathy, anxiety, use of memantine or anti-psychotics, and scores on the Clock Drawing Test were significantly associated with length of sleep in this sample.

1. Introduction

Sleep length and architecture deteriorate with normal aging, mild cognitive impairment and dementia, and could represent potential markers of progressive cognitive impairment [1,2]. Nonetheless, insomnia is not a normal aspect of aging [3]. Recurrently observed sleep disturbances in patients with dementia due to Alzheimer's disease (AD) include difficulty to initiate sleep, fragmented sleep with frequent awakenings, decreased total sleep time with early awakening, waking up at night and thinking that it is daytime, night-time wandering, daytime napping, increased latency to first rapid eye movement (REM) sleep episode, decreased slow-wave sleep, impaired sleep efficiency, sleep-disordered breathing (mostly obstructive sleep apnoea) and sundowning [3,4]. Regarding characterisation of the decrease in total sleep time, provisional diagnostic criteria for insomnia in patients with AD were designed in 2003 [5], based on the reduction of 25% of total nocturnal sleep relative to the premorbid nocturnal sleep pattern, or fewer than 6 hours of sleep at night.

Sleep disturbances increase with advancing dementia severity, and may predict a faster cognitive decline, mostly in the mild to moderate stages of AD [6]. Insomnia may also lead to more patient institutionalisation, increase risk of falls and mortality, and impact caregiver burden [3,5,7]. Other non-cognitive complications may result from sleep-disordered breathing, which increases cardiovascular risk and agitation, and is not unusual in patients with AD [5,7,8].

A recent actigraphic study showed that cerebrospinal fluid Aβ42 levels were associated with worse sleep efficiency and more frequent napping (three or more days per week) in the preclinical stages of AD [9]. This is particularly important considering that

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Aβ increases during wakefulness and decreases during sleep, but it does not seem possible at the moment to objectively address whether poor sleep causes AD or, *vice versa*, if dementia is the cause of sleep disruption.

The suprachiasmatic nucleus of the hypothalamus is the primary circadian pacemaker in the mammalian brain, and is indirectly connected to the ventrolateral preoptic area [10]; both of these hypothalamic structures are susceptible to age-related volumetric reductions, possibly contributing to increased sleep fragmentation and slow-wave sleep deficits found in the elderly [10,11]. The hypothalamic hypocretin system has been shown to be affected in severe AD, with decreased neuronal numbers and lower cerebrospinal fluid hypocretin-1 levels, which may be related to the amount of daytime napping [12]. Slow-wave sleep has been consistently implicated in declarative memory consolidation, a process that seems to involve connections between the hippocampus and neocortical areas [2]. Moreover, cholinergic dysfunction originating in the nucleus basalis of Meynert and mesopontine neurons of the pedunculopontine tegmentum and the laterodorsal tegmentum has been associated with REM sleep deficits in patients with AD [3,10].

Correlations between sleep satisfaction and neuropsychiatric symptoms during cognitive decline in AD are still imprecise. An earlier preliminary study from our group [13] confirmed that behavioural symptoms and low education levels are associated with more sleep complaints in patients with AD, and also that sleep satisfaction and length of sleep are closely related. In this study, with a more comprehensive evaluation of a larger sample, we sought to investigate which factors might be related to sleep satisfaction in patients with AD.

2. Subjects and methods

This is a cross-sectional study in which consecutive outpatients with AD [14] in different stages were recruited from the Behavioural Neurology Section of Hospital São Paulo, Brazil from November 2010 to February 2013 (28 months). After diagnostic confirmation, they were assessed for age, sex, education level, marital status, estimated age of onset of the dementia syndrome, quantification of current alcohol consumption and/or smoking, use of cholinesterase inhibitors or anti-depressants, use of antipsychotics or anti-epileptic drugs, number of different medications taken daily, body mass index, and scores on the Neuropsychiatric Inventory [15], Mini-Mental State Examination [16], Severe Mini-Mental State Examination [17], Clinical Dementia Rating (CDR) [18], a 15-item Clock Drawing Test (free drawing) [19], the Index of Independence in Activities of Daily Living [20], Lawton's Scale for Instrumental Activities of Daily Living [21], and the Brazilian version of the Zarit Caregiver Burden Interview [22]. Patients were asked if their sleep was satisfactory (yes or no), what factors might interfere with it, and the mean amount of time slept each day, with confirmation by their caregivers. The length of sleep had to be as precise as possible, including daytime naps, and excluding eventual time spent in bed without sleeping. In case patients were unable to describe their sleep, preference was given to caregiver reports. All cognitive evaluations and body mass index measurements were conducted on weekdays in the morning by the same examiner (F.F.O.).

Diagnosis of AD was in accordance with National Institute on Aging – Alzheimer's Association criteria [14]. Obesity was diagnosed when the body mass index was over 30 kg/m^2.

For the validated version of the Clock Drawing Test [19] that was used in this study, patients were instructed to freely draw a clock that said 11:10, setting the hands and numbers on the face (repetition was allowed). Scoring comprised the following 15 items, each scored as 0 or 1: outer circle present and closed; acceptable circle diameter; intact sequence 1–12, with no omissions or intrusions; only Arabic numerals; correct sequential order of the numerals; paper not rotated for number placement; proper symmetrical spacing; all numbers inside the circle; only two hands present; any mark to indicate the hour; any mark to indicate the minute; minute hand longer than hour hand; no pointless intrusions; both hands connected, or up to 2 mm space between them; and the centre of the clock drawn or inferred where hands meet.

The Index of Independence in Activities of Daily Living [20] reflects behavioural levels of six sociobiological functions: bathing, dressing, toileting, transfer, continence, and feeding. Each function was scored as 0 for dependency or 1 for independence, according to information from caregivers, with an index total of 0 to 6. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of Lawton's Scale for Instrumental Activities of Daily Living [21] was employed, with scores for using the telephone, getting to places beyond walking distance, grocery shopping, meal preparation, housekeeping, doing handyman work, doing laundry, taking own medications, and handling finances. This information had to be obtained from caregivers, with a possible total score between 9 and 27.

After blood samples were collected from all patients in tubes with EDTA 0.1%, genomic DNA was extracted for genotyping. APOE haplotypes were determined for all patients (single nucleotide polymorphisms rs7412 and rs429358 assessed by way of real-time polymerase chain reactions using TaqMan SNP Genotyping Assays (Life Technologies, Carlsbad, CA, USA). Real-time polymerase chain reactions (PCR) were undertaken on the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) following the standard protocols of the manufacturer.

Statistical comparisons among groups according to APOE haplotypes or sleep satisfaction were conducted by way of Mann–Whitney *U* test (two groups) or Kruskal–Wallis test (more than two groups). A multiple regression model was employed for correlations among the continuous variables that might impact the daily quantity of sleep (dependent variable) with 13 degrees of freedom, and also independently for correlations among each item from the Neuropsychiatric Inventory and the daily quantity of sleep with 10 degrees of freedom. Fisher's exact test was employed for comparisons between categorical variables. The threshold of significance was set at $p < 0.05$.

This study is part of the research project 1067/10 (CAAE 0540.0.174.000-10) approved by the Ethics Committee of Hospital São Paulo, Federal University of São Paulo (UNIFESP), on August 2010. All invited patients and their respective caregivers agreed to participate on the research and signed the informed consent form before the evaluation, with no exceptions.

3. Results

A total of 217 patients were included, with 147 females (67.7%) and 70 males (32.3%); 109 (50.23%) were married, while six (2.76%) were divorced, 19 (8.76%) were single, and 83 (38.25%) were widowers; 56 (25.8%) had a history of alcohol consumption, and 11 (5.1%) were regularly drinking at the time of the survey; 79 (36.4%) had a smoking history, and 14 (6.5%) were regular smokers at the time of the survey. Obesity was diagnosed in 36 patients (16.6%). Detailed demographic and test results, along with statistical differences according to sleep satisfaction, are found in Table 1.

Table 2 shows results according to APOE haplotypes, with 114 APOE4+ and 103 APOE4− cases. Earlier onset of dementia was correlated with APOE4+ in patients with CDR of 2.0 (n = 104, $p = 0.019$) and with the E4/E4 haplotype in patients with CDR of 1.0 (n = 83, $p = 0.007$). APOE haplotypes had no significant

Table 1
Demographic results and statistical comparisons according to the presence or absence of sleep complaints

Variable (units)	Mean ± SD (n = 217)	Sample range	Mean ± SD for each variable according to sleep satisfaction		Mann–Whitney U[a] test	
			Satisfied (n = 179)	Unsatisfied (n = 38)	Statistic	*p* value
Age at examination (years old)	78 ± 6.1	60–94	78 ± 6.2	78 ± 5.8	3131.5	0.443
Age of dementia onset (years old)	73.15 ± 6.8	52–88	73.22 ± 6.9	72.83 ± 6.4	3288.5	0.749
Schooling (years)	4.21 ± 3.7	0–15	4.31 ± 3.7	3.74 ± 3.6	2959.5	0.197
Daily length of sleep (hours/day)	8.99 ± 1.9	4–14	9.19 ± 1.7	8.05 ± 2.4	2524.0	0.011
Body mass index (kg/m^2)	25.75 ± 4.3	14.28–41.62	25.66 ± 4.2	26.19 ± 4.8	3560.5	0.650
Different medications taken daily	4.52 ± 2.5	0–12	4.55 ± 2.4	4.39 ± 3.1	3118.0	0.417
Current alcohol consumption (l/year)	1.67 ± 11.3	0–120	2.03 ± 12.4	0.00 ± 00.0	3192.0	0.118
Current smoking (packs/year[b])	14.38 ± 62.1	0–365	13.88 ± 61.3	16.71 ± 66.4	3459.0	0.698
Neuropsychiatric Inventory (0–120 points)	22.61 ± 16.6	0–87	21.01 ± 15.1	30.29 ± 20.7	4135.0	0.009
Mini-Mental State Examination (0–30 points)	15.64 ± 5.8	0–29	15.55 ± 5.5	16.03 ± 7.1	3624.0	0.525
Severe Mini-Mental State Examination (0–30 points)	26.43 ± 4.9	0–30	26.73 ± 4.3	25.01 ± 6.6	3122.5	0.420
Clock Drawing Test (0–15 points)	6.26 ± 4.5	0–15	6.25 ± 4.4	6.32 ± 5.2	3346.0	0.875
Index of Independence in Activities of Daily Living (0–6 points)	5.01 ± 1.6	0–6	5.02 ± 1.6	4.97 ± 1.5	3269.0	0.672
Lawton's Scale for Instrumental Activities of Daily Living (9–27 points)	14.21 ± 4.7	9–27	13.97 ± 4.7	15.32 ± 5.6	3757.0	0.308
Brazilian Version of the Zarit Caregiver Burden Interview (0–56 points)	16.58 ± 10.7	0–54	16.08 ± 10.3	18.89 ± 11.9	3812.5	0.241

[a] Mann–Whitney U test was applied for groups according to sleep satisfaction.
[b] 1 pack = 20 cigarettes.
SD = standard deviation.

association with daily medication intake or scores on the Neuropsychiatric Inventory.

Concerning sleep complaints, 179 patients (82.5%) answered that their sleep was satisfactory, while 38 (17.5%) were unsatisfied, and 13 (5.9%) self-reported that they slept on average fewer than 6 hours per night. No differences among sex ($p = 0.13$) or marital status (married *versus* non-married, $p = 0.48$) were found with regard to sleep satisfaction. Patients who were APOE4− had more sleep complaints than patients who were APOE4+ although this was not significant ($p = 0.59$), with no significant difference in the length of their sleep ($p = 0.13$). For all patients, regardless of APOE haplotypes, length of sleep ($p = 0.011$, Fig. 1) and lower scores on the Neuropsychiatric Inventory ($p = 0.009$, Fig. 2) were significantly associated with sleep satisfaction.

Table 3 shows results for multiple factors that might affect length of sleep (F ratio = 2.3582; $p = 0.0061$; multiple R = 0.3622; adjusted squared multiple R = 0.0756; standard error of estimate = 1.796). Significance was found for an increase of 0.098 hours of sleep for each point increase in the Clock Drawing Test ($p = 0.015$), and for a decrease of 0.106 hours of sleep for each point increase in Lawton's Scale for Instrumental Activities of Daily Living ($p = 0.003$). Also, independence for Instrumental Activities of Daily Living was directly correlated with body mass index ($p < 0.01$), higher education level ($p < 0.01$) and the Clock Drawing Test ($p < 0.001$), and inversely correlated with caregiver burden ($p < 0.003$), alcohol consumption ($p < 0.017$) and smoking ($p < 0.005$).

Table 4 shows results for behavioural scores, with higher mean scores for apathy and anxiety (F ratio = 2.5676; $p = 0.0062$; multiple R = 0.3329; adjusted squared multiple R = 0.0677; standard error of estimate = 1.804). Significance was found for an increase of 0.075 hours of sleep for each point increase in apathy scores ($p = 0.014$), and for a decrease of 0.079 hours of sleep for each point increase in anxiety scores ($p = 0.015$).

Overall, 170 patients (78.34%) were using cholinesterase inhibitors at the time of the survey: 60 used rivastigmine, 58 used donepezil, and 52 used extended-release galantamine; 52 patients (23.96%) were treated with memantine, while 88 (40.55%) used anti-depressants; 53 patients used anti-psychotics (24.42%), namely quetiapine (n = 42), risperidone (n = 10) and olanzapine (n = 1); and 19 patients used anti-epileptic drugs (8.76%), mostly carbamazepine (n = 7) and valproic acid (n = 6). No differences were found for length of sleep with regard to use of rivastigmine, donepezil, extended-release galantamine, or no use of cholinesterase inhibitors ($p = 0.64$), nor for use or non-use of anti-depressants ($p = 0.24$) or anti-epileptic drugs ($p = 0.61$). Nevertheless, patients who were treated with memantine slept longer (mean 9.52 ± 1.9 hours *versus* 8.82 ± 1.8 hours, $p = 0.02$), although they did not have fewer complaints than patients who did not use memantine ($p = 0.41$). Patients who used anti-psychotics also slept longer than those who did not (mean 9.55 ± 2.1 hours *versus* 8.81 ± 1.8 hours, $p = 0.0095$).

4. Discussion

This is a cross-sectional study, with no power to establish causal relations; therefore, only associations may be deduced from the results.

Table 2
Genetic results and comparisons according to characteristics of sleep

APOE haplotypes	n	Mean ± SD for age of dementia onset (years old)	Sleep satisfaction		Mean ± SD for length of sleep (hours/day)
			Satisfied, n (%)	Unsatisfied, n (%)	
APOE E4/E4	26	69.4 ± 6.8	19 (73.1%)	7 (26.9%)	8.96 ± 1.9
APOE E4/E3	81	73.5 ± 6.3	72 (88.9%)	9 (11.1%)	9.28 ± 1.8
APOE E4/E2	7	74.0 ± 2.3	5 (71.4%)	2 (28.6%)	9.29 ± 1.7
APOE E3/E3	93	73.7 ± 7.2	75 (80.6%)	18 (19.4%)	8.69 ± 1.9
APOE E3/E2	10	74.3 ± 6.5	8 (80.0%)	2 (20.0%)	9.30 ± 2.4

SD = standard deviation.

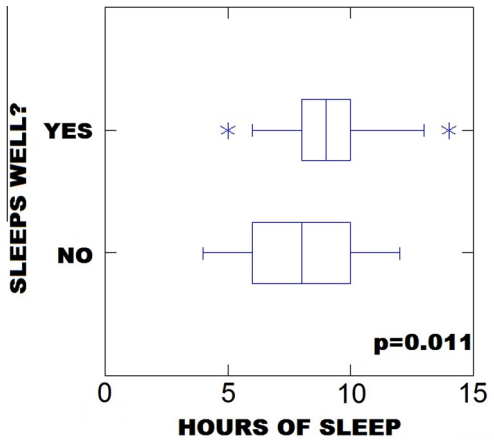

Fig. 1. Boxplot showing the median, 25th–75th percentiles, and the range of length of sleep according to sleep satisfaction. Asterisks represent outliers.

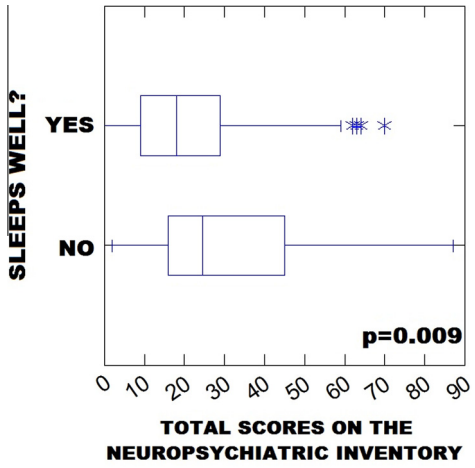

Fig. 2. Boxplot showing the median, 25th–75th percentiles, and the range of total scores on the Neuropsychiatric Inventory according to sleep satisfaction. Asterisks represent outliers.

The proportion of self-reported sleep dissatisfaction in this sample was 17.5%. Patients with AD tend to have more sleep complaints than non-demented elderly people or patients with mild cognitive impairment, but frequency of sleep dissatisfaction is widely variable across studies [23], ranging from less than 20% to more than 80% depending upon the criteria employed for sleep disorders [24,25]. Sleep disturbances may appear very early in the dementia course, or even during the phase of mild cognitive impairment [1], impacting memory disruption [2]. Patients with AD and mild cognitive impairment have a shortening of REM sleep together with increased fragmentations of slow-wave sleep relative to healthy elderly people, and these manifestations seem to be uncorrelated with memory performance, but more noticeable in those who are APOE4+ [10]. In the general middle-aged population, APOE4+ haplotypes have been associated with sleep-disordered breathing according to polysomnographic measurements of apnoea–hypopnea index $\geqslant$15% [8]. Melatonin levels have also been shown to be changed according to APOE haplotypes in patients with AD, suggesting an APOE-mediated regulation of the sleep-wake cycle [10,11].

Though non-significant, patients who were APOE4− had more sleep complaints regardless of behavioural symptoms or length of sleep, but neuropsychiatric symptoms were also non-significantly more frequent among such patients. The APOE4− group had a later onset of dementia, with a probable lengthier dementing process than APOE4+ patients, a fact that could possibly contribute to more sleep dissatisfaction. Other studies with smaller samples have shown more frequent sleep disturbances according to impaired cognition in APOE4− patients with mild cognitive impairment [10] and AD [7,11], including increases in wake after sleep onset and declines in total sleep time and sleep efficiency. Further longitudinal studies are needed to better understand the role of APOE haplotypes over sleep and other neuropsychiatric symptoms in patients with AD.

Confirming our earlier results [13] and results from other studies [25] there was a close correlation between sleep satisfaction and length of sleep. Education level was non-significant in the current sample, but higher scores on the Clock Drawing Test were highly significant for length of sleep; this may reflect an indirect association with education, in view of the high correlations usually found between educational levels and scores on this test [19].

All neuropsychiatric symptoms were more frequent for patients who had more sleep complaints. However, regarding sleep quality, dysphoria, anxiety and irritability were the most significant factors to negatively correlate with satisfaction. Dysphoria has already been noted as the most important neuropsychiatric symptom to impact sleep in patients with AD [4]. Agitation, anxiety and irritability have also been established as relevant factors in a methodologically different study [24]. Our results also confirm the reliability of the 10 item Neuropsychiatric Inventory [15] to assess

Table 3
Multiple linear regression for factors related to length of sleep

Variable (units)	β	95% confidence interval		t	*p* value
		Lower	Upper		
Daily length of sleep (hours/day)	11.600	7.548	15.652	5.645	–
Age at examination (years)	−0.006	−0.047	0.036	−0.267	0.790
Education (years)	0.030	−0.043	0.102	0.798	0.426
Body mass index (kg/m^2)	0.017	−0.042	0.077	0.573	0.567
Different medications taken daily	−0.007	−0.114	0.099	−0.132	0.895
Current alcohol consumption (l/year)	−0.016	−0.038	0.006	−1.454	0.147
Current smoking (packs/year[a])	−0.003	−0.007	0.001	−1.450	0.149
Neuropsychiatric Inventory (0–120 points)	−0.012	−0.030	0.005	−1.431	0.154
Mini-Mental State Examination (0–30 points)	−0.058	−0.136	0.020	−1.470	0.143
Severe Mini-Mental State Examination (0–30 points)	−0.011	−0.093	0.072	−0.255	0.799
Clock Drawing Test (0–15 points)	0.098	0.019	0.176	2.454	0.015
Index of Independence in Activities of Daily Living (0–6 points)	−0.047	−0.242	0.148	−0.476	0.634
Lawton's Scale for Instrumental Activities of Daily Living (9–27 points)	−0.106	−0.176	−0.036	−3.003	0.003
Brazilian Version of the Zarit Caregiver Burden Interview (0–56 points)	−0.002	−0.029	0.025	−0.163	0.871

[a] 1 pack = 20 cigarettes.

Table 4
Results from behavioural domains of the Neuropsychiatric Inventory according to sleep complaints and length of sleep

Variable[a]	Mean scores (n = 217)	Mean ± SD for each domain according to sleep satisfaction		Mann–Whitney U test[b]		Multiple linear regression for behavioural symptoms related to length of sleep				
		Satisfied (n = 179)	Unsatisfied (n = 38)	Statistic	*p* value	β	95% confidence interval		t	*p* value
							Lower	Upper		
Daily length of sleep	–	–	–	–	–	9.074	8.626	9.522	39.944	–
Delusions	1.590	1.49 ± 2.8	2.05 ± 3.6	3616.5	0.488	0.005	−0.087	0.097	0.109	0.913
Hallucinations	1.212	0.99 ± 2.3	2.26 ± 3.7	3968.5	0.061	0.051	−0.057	0.159	0.927	0.355
Agitation	2.576	2.47 ± 3.4	3.08 ± 3.8	3674.5	0.420	−0.041	−0.126	0.045	−0.941	0.348
Dysphoria	2.323	2.01 ± 3.1	3.79 ± 3.8	4423.5	0.002	−0.009	−0.087	0.068	−0.239	0.811
Anxiety	3.074	2.75 ± 3.9	4.61 ± 4.7	4163.0	0.022	−0.079	−0.142	−0.015	−2.444	0.015
Euphoria	1.124	1.11 ± 2.7	1.21 ± 2.3	3821.5	0.115	0.064	−0.035	0.164	1.279	0.202
Apathy	4.604	4.55 ± 4.3	4.87 ± 4.5	3535.5	0.696	0.075	0.016	0.134	2.491	0.014
Disinhibition	1.184	1.03 ± 2.4	1.89 ± 3.3	3795.5	0.163	0.061	−0.048	0.171	1.104	0.271
Irritability	2.687	2.39 ± 3.1	4.08 ± 4.4	4160.0	0.026	−0.062	−0.152	0.028	−1.360	0.175
Aberrant motor behaviour	2.258	2.22 ± 3.9	2.45 ± 4.1	3354.0	0.875	−0.047	−0.111	0.017	−1.461	0.145

[a] The score of each behavioural domain ranges from 0 to 12.
[b] Mann–Whitney U test was applied for groups according to sleep satisfaction.
SD = standard deviation.

psychopathology in patients with AD, while the expanded 12 item Neuropsychiatric Inventory [26] may not be as suited for such patients as it is for patients with depression, who are prone to weight loss and sleep disturbances.

Apathy was the most frequently reported neuropsychiatric symptom for patients in all stages of AD, according to most studies [4,26]. Since apathy impacts functional independence, the decreased length of sleep found for patients with higher independence in Instrumental Activities of Daily Living could correspond to a lesser degree of apathy. A recent actigraphic study [27] showed that apathy is related to higher wake after sleep onset and lower daytime mean motor activity, consistent with diminished amplitude of circadian processes, though total sleep time was no different from patients without apathy. Another study [28] found worse cognition and functionality for patients who spent more than 6 hours in bed per night.

Hallucinations are a poor prognostic factor for patients with AD [6]. Considering that this sample had low mean scores for hallucinations, with a marginally significant association with length of sleep, it is possible that some patients with hallucinations had already died before the evaluation, thus providing a confounding factor that led to the underestimation of the importance of hallucinations for these results [35].

Higher schooling and body mass index were correlated with higher independence for Instrumental Activities of Daily Living. Weight loss is a manifestation of brain dysfunction; hence, patients are expected to be losing more weight in the later stages of AD, when they are invariably less independent [29,30]. Caregiver burden was inversely correlated with independence for activities of daily living, as expected.

Patients who were treated with memantine slept longer regardless of sleep satisfaction. Since memantine was only prescribed to patients in moderate and severe dementia stages, this result corresponds to the stages in which apathy tends to be more prominent. Later stages of dementia are also when most neuropsychiatric symptoms tend to increase, leading to more widespread use of anti-psychotics, which were also correlated with a longer length of sleep. Even though modulation of sleep quality by treatment with memantine or cholinesterase inhibitors was not found in our sample, cholinergic drugs have been associated with REM sleep enhancement correlating with cognitive improvement by such treatment [31,32]. Anti-psychotics such as risperidone may increase brain synthesis of dopamine, improving sleep-wake patterns and behavioural symptoms like agitation, aberrant motor behaviour, hallucinations and delusions [33,34].

The major strength of this study resides in the broad neuropsychiatric evaluation that was undertaken by all patients, allowing for multiple correlations among all parameters, with a uniform and mostly unbiased assessment of insomnia. However, it lacks a more objective documentation of sleep length and its disorders, such as an actigraphic or polysomnographic analysis, as well as a validated instrument for evaluation of sleep, such as the Sleep Disorders Inventory [25]. In spite of these caveats, our results were not too different from studies with more objective assessments of sleep, thus confirming the reliability of our data. Nevertheless, further studies with more objective measurements of sleep are required to longitudinally investigate the impact of *APOE* haplotypes and cognitive-behavioural manifestations over sleep satisfaction and quality of life in patients with AD.

Conflicts of Interest/Disclosures

F.F.O. receives personal compensation for acting as a Healthcare Council Member for Gerson Lehrman Group. P.H.F.B. has received personal compensation for acting as a consultant for Janssen, Lilly, Novartis, Pfizer and Support. M.A.C.S. receives support for scholarly activities from the following Brazilian public agencies for research: The State of São Paulo Research Foundation (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). E.S.C. has nothing to declare.

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